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Right Heart Adaptation to Pulmonary Arterial Hypertension: Physiology and Pathobiology: A Systematic Review

Hazrat Ullah Khan[1], Malik Faisal Iftekhar[2] ✉, Syeda Huma Khizar[3], Farhat Rehman[4], Marina Hidayat[5], Abdul Samad[6]

[1]Department of Cardiology, Ayub Teaching Hospital, Abbottabad - Pakistan [2]Department of Cardiology, Lady Reading Hospital, Medical Teaching Institute, Peshawar - Pakistan [3]Department of Physiology, KMU Institute of Medical Sciences, Kohat - Pakistan [4]Department of Physiology, Bacha Khan Medical College, Mardan - Pakistan [5]Department of Physiology, Peshawar Medical College, Peshawar - Pakistan [6]Department of Physiology, Pak International Medical College, Peshawar - Pakistan

Corresponding Author:
Malik Faisal Iftekhar
Department of Cardiology
Lady Reading Hospital,
Medical Teaching Institute,
Peshawar - Pakistan
Email: malikfaisal6@gmail.com

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a chronic disease affecting the pulmonary vasculature and right ventricular (RV) function, leading to right heart failure (RHF). Effective management of RHF in PAH patients is critical due to its impact on prognosis and survival.

Objective: To evaluate the current knowledge on RV pathobiology in PAH and highlight the importance of managing RHF in these patients.

Methodology: A comprehensive review of existing literature was conducted, focusing on RV function, adaptive and maladaptive remodeling, clinical presentation, prognostic indicators, and therapeutic strategies for RHF in PAH. Key sources included peer-reviewed journals, clinical trials, and expert guidelines.

Results: The review indicates that RV dysfunction in PAH is characterized by adaptive and maladaptive remodeling, leading to progressive RHF. Clinical indicators of RHF include elevated systemic venous pressure, fluid retention, and exercise limitation. Prognostic factors such as RV ejection fraction, tricuspid annular plane systolic excursion, and cardiac biomarkers are crucial for outcome prediction. Current therapies focus on pulmonary vasodilation and targeted RV treatment, with potential benefits from metabolic regulation and novel interventions.

Conclusion: Effective management of right heart failure in pulmonary arterial hypertension patients is crucial for improving prognosis and survival. Understanding the pathobiology of right ventricular dysfunction and its clinical implications can guide the development of targeted therapies. Future research should focus on novel treatment strategies and metabolic regulation to optimize patient outcomes in PAH-associated RHF.

Keywords: Pulmonary Arterial Hypertension; Right Ventricular Dysfunction; Right Heart Failure; RV Remodeling

Introduction

The long-term illness known as pulmonary arterial hypertension (PAH) affects the heart and the pulmonary blood arteries. Right ventricular (RV) function plays a major role in the survival of patients, although firstly PAH primarily impacts the pulmonary vasculature.[1-6] The right ventricle thickens and becomes more contractile in order to handle the extra afterload.[7-19] The majority of people eventually acquire RV dysfunction in spite of these adjustments. This article highlights the data in favor of managing right heart failure (RHF) in patients with PAH and analyzes the state of knowledge on RV pathobiology in PAH. Additionally, it talks on the priority for subsequent RV studies regarding PAH. The emphasis is on RHF in relation to PAH, but it's also critical to remember that RV function plays a significant role in predicting outcomes for individuals with congenital heart disease, severe lung disease, and left-sided heart failure.[20]

In those who have PAH, right heart failure (RHF) is a complicated clinical condition marked by raised systemic venous pressure during exercising or at rest as a result of raised right ventricular (RV) afterload, as well as insufficient blood supply. Retention of fluid and restriction of exercise are the main clinical indicators of RHF. Workout restriction is the first and most indicative characteristic of refractory heart failure (RHF).[8,14,21] It is associated with a reduced peak cardiac index,[22-24] or diminished flow reserve during physical activity. Decreased peripheral blood flow can raise the release of lactate, which exacerbates muscular exhaustion and limits exercising. Surviving a supraventricular tachycardia can also be a problem for 12% of individuals with PAH or incurable thromboembolic pulmonary hypertension, worsening their clinical status and limiting their ability to workout.[25] Even though it is less frequent, fainting indicates serious flow reserve constraints. Like left-sided heart failure, RHF can lead to hyponatremia[26] and persistent kidney damage. According to findings by Shah and colleagues[27], people with PAH who have persistent kidney disease have higher right atrial pressure, a higher chance of dying or requiring a transplant. Bad outcomes after acute RHF are also linked to acute renal damage.[28] Although PAH and RHF patients commonly experience congestive hepatopathy, cirrhosis develops as a late-stage consequence of severe RHF.

Clinical Presentation and Prognosis of Acute Right Heart Failure in PAH

Acute heart failure episodes are another possibility for individuals with PAH. According to recent research, the short-term death rate for individuals with PAH who require hospitalization due to acute right heart failure (RHF) can reach up to 40%.[29-32] A lower percentage of patients with acute RHF will come with low cardiac output syndrome, necessitating inotropic or vasopressor support, even if the majority are hospitalized for congestive symptoms necessitating treatment with diuretics.[29,30] The primary cause mortality for patients with PAH is progressive RHF, however unexpected, abrupt mortality is also possible. In research by Hoeper and colleagues, 17% of cardiac arrests in which resuscitation was tried were due to abrupt death. First ECGs revealed bradycardia in 45 percent of those who suffered cardiopulmonary arrest, electromechanical dissociation in 28%, asystole in 15%, ventricular fibrillation in 8%, and abnormal rhythms in 4% of patients.[33]

The four phases of chronic left heart failure are usually identified as follows: stage A is at risk of heart failure, stage B is asymptomatic heart dysfunction, stage C is symptomatic heart failure, and stage D is end-stage heart failure. Although numerous individuals with advanced RHF (stage D) have a chance for reverse remodeling after lung transplantation, this classification could be applicable to these patients.[34] Furthermore, despite the fact that the left and right ventricles are frequently seen as separate entities, they are actually linked by the pericardium, shared myocardial fibers, and the interventricular septum. Due to this ventricular dependency, people who have RHF often have anomalies in the left ventricle's relaxation and, in cases of greater severity, left ventricular systolic dysfunction.[2,20,35] Additionally, electrophysiological change in the left ventricle has been addressed by a recent investigation.[36]

Pathobiology of Right Heart Failure Syndrome in Pulmonary Arterial Hypertension

The complex procedure of right ventricular '(RV) remodelling' in patients with pulmonary arterial hypertension (PAH) is impacted by the degree of pulmonary vascular disease as well as the interplay among myocardial metabolism, coronary perfusion, and neurohormonal activation. (Figure 1)[6,20,37-45] The pace and duration of pulmonary hypertension start, its root causes, and possibly genetic and epigenetic variables all have an impact on RV adaptability.

Adaptive and maladaptive remodelling are the two forms of ventricular remodelling that are frequently distinguished in experimental studies using morphometric and molecular characteristics. Adaptive remodelling, shown in diseases such as Eisenmenger syndrome, entails increased concentric hypertrophy with a higher mass-to-volume ratio and retained systolic and diastolic function. On the other hand, maladaptive remodelling, which is typical of 'PAH associated with connective tissue illnesses or idiopathic PAH', is characterized by eccentric hypertrophy, which results in poor systolic and diastolic performance.[9,46] Tricuspid regurgitation, which frequently results from annular dilatation, can impair flow reserve and cause unfavourable ventricular remodelling. Furthermore, those

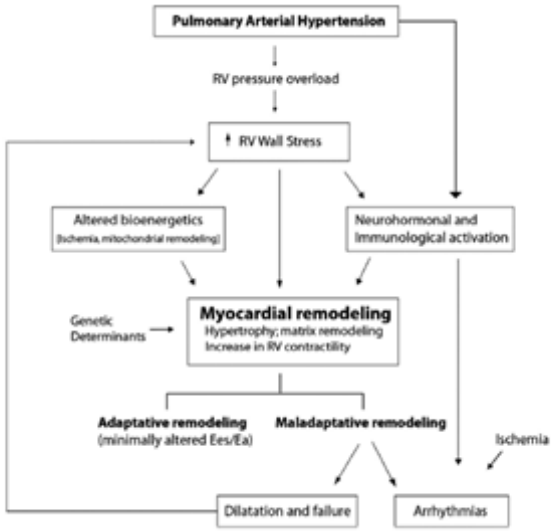

Figure 1. Pathophysiology of RV Dysfunction in PAH

who have maladaptive remodelling and severe RHF are more likely to exhibit right-to-left shunting via a patent foramen ovale.[47]

According to recent studies, significant dysfunction and maladaptive remodelling are indicated by RV dyssynchrony.[48-54] In PAH, late systolic leftward septal movement results from the 'RV free wall continuing to contract while the left ventricle' approaches early diastole. Mechanically stressed myocytes lengthen their contraction time and action potential, which exacerbates dyssynchrony between the left and right ventricles. A worse prognosis is linked to this dyssynchrony, which intensifies with RV wall stress.[55]

Ventricular Remodelling Under Pressure Overload

There are a few significant variations between how pressure overload affects the ventricles on the right and left side. Comparing to 'the pressure-overloaded left ventricle, which develops in situations like systemic hypertension or aortic stenosis', ventricular enlargement happens significantly earlier in PAH. This is partially caused by the narrower RV wall, which results in raised RV wall stress for a given pressure rise.[56-59] Furthermore, under pressure overload, fibrosis in the RV is much less widespread; it usually affects less than '10% of the ventricular volume and is frequently limited to the RV-septal insertion' sites. Individuals with significant systemic hypertension or aortic stenosis, on the other hand, have more extensive myocardial fibrosis. Although the 'right ventricular ejection fraction (RVEF) is significantly reduced at the time of transplantation',[60-63] numerous individuals with severe RHF can regain RV function due to this minimal fibrosis in PAH. Investigation is still ongoing to determine which individuals could benefit from heart-lung transplantation while others are unlikely to regain RV function after transplantation.[64]

The Concept of Ventriculoarterial Coupling and the Cardiopulmonary Unit in PAH

The right side of the heart and the blood vessels in the lungs should be seen as a single cardiovascular unit instead of as two distinct organs, according to recent PAH study.[5] This viewpoint is important from a physiological and therapeutic standpoint. Research has indicated that the capacity of the RV to improve its contractility in reaction to elevated afterload is essential for RV adaptation to PAH.[43,65] The most reliable metric of "ventriculoarterial coupling" is the ratio of ventricular elastance to arterial elastance, which characterizes the link between ventricular contractility and afterload. It is thought that the ideal ratio for the RV is likewise among 1.5 and 2.0, showing a balance between RV mechanical labor and usage of oxygen, even though this idea is mostly taken from investigations on the left ventricle.[5,43,66] However enhanced RV myocardial contractility, Kuehne and colleagues showed a relationship between impaired RV pump function and persistent RV pressure overload in PAH. Poorer ventriculoarterial coupling between individuals with scleroderma-associated PAH compared to those with idiopathic PAH with equal afterload has been validated by additional research employing ventriculoarterial measurements.[67]

Clinical Estimation of Right Ventricular Afterload

Basic measurements including arterial elastance, 'pulmonary vascular resistance, and pulmonary arterial

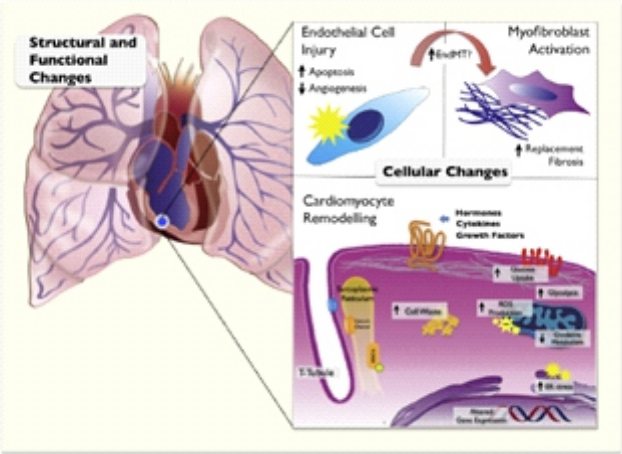

Figure 2. Molecular Pathways Involved in RV remodelling in PAH

compliance are used' in clinical settings to evaluate RV afterload. While pulmonary vascular resistance and pulmonary artery compliance characterize the 'resistive and pulsatile loads of the pulmonary circulation, respectively, arterial elastance is an indicator of afterload during pressure-volume loop analysis'. These elements are essential to comprehending the right ventricle's function. Research shows that the pulsatile component makes up the remaining 23% of the overall hydraulic RV power, with the resistive component making up around 77% of the entirety.[68] Because of the peculiarities of the pulmonary circulation in comparison to the systemic circulation, this distribution is comparatively consistent.

Resistance and compliance are negatively correlated during treatment and over time in the pulmonary circulation. For the same reason, total compliance is also influenced by the pulmonary system's resistive vessels. (Figure 2)[69,70] On the contrary, the pulsatile load relative to the resistive load can be raised by elevated pulmonary capillary wedge pressure, which can lower the resistance-compliance time constant in the pulmonary system and increase the net RV afterload.[71-72]

Comprehensive Understanding of Right Ventricular Afterload

Conventional afterload indices are helpful in clinical settings, but a more physiologic definition would take into account all the variables that affect the stress on the myocardium during systole. This comprises the wall thickness, ventricular geometry, chamber expansion, and ventricular pressure. Furthermore, by offering a different, less resistive channel, conditions like tricuspid regurgitation and right-to-left shunting (via a patent foramen ovale, septal defect, or atrial septostomy) can lessen afterload.[73-75] Creating thorough afterload models could improve our ability to forecast how right heart failure (RHF) will advance. The present emphasis of investigations focuses on biophysical models that provide novel insights into the cardiac adaptation to pulmonary arterial hypertension (PAH) by connecting local cardiac myofiber mechanics to global cardiovascular dynamics.[76,77] The elements causing passive end-diastolic ventricular wall stress are referred to as pre-load. In treating individuals who have acute RHF, optimal pre-load improves cardiac output without significantly impairing renal function or generating systemic congestion.[27]

Myocardial Metabolism and Inflammation in Right Heart Failure

Myocardial metabolism changes in right heart failure (RHF) from fatty acid oxidation to glycolysis. As glycolysis uses a smaller amount of oxygen than fatty acid oxidation, this metabolic transition is believed to be a defense mechanism. This alteration aids the overworked heart in meeting the heightened demands on metabolism.[78-79] Yet, the shift from compensatory right ventricular (RV) hypertrophy to maladaptive remodelling might be facilitated by lowered activity of the mitochondria, which results in a shift from aerobic to anaerobic metabolism.[80]

Vascular endothelial growth factor (VEGF) signals can be compromised by inadequate capillary network adaptation, which can lead to myocardial ischemia and impede the hypertrophic response. Heart failure is further exacerbated by diminished ventricular compliance, which is a result of increasing myocardial fibrosis seen in RV collapse.[81-85]

The function of inflammation in the right ventricle, which is overwhelmed with pressure, is highlighted by recent study. Research on both humans and animals has shown that during acute elevations in afterload, neutrophils infiltrate the RV myocardium, but macrophages appear more pronounced during gradual remodelling in chronic

pulmonary hypertension.[86-92] The involvement of leukotrienes, T-regulatory cells, and macrophages in the development of RHF among those with pulmonary arterial hypertension (PAH) are being investigated in a current study.[93-97]

Evaluation of Right Heart Size and Function: From Resting Parameters to Dynamic Evaluation

When it comes to treating patients with pulmonary arterial hypertension (PAH), evaluating the right heart is essential.[98] The best possible technique for assessing right ventricular (RV) mass, volume, and ejection fraction (RVEF) is magnetic resonance imaging (MRI), even though echocardiography is still the principal instrument used in clinical settings. Moreover, regurgitant volumes can be measured, focal scar tissue can be found using delayed improvement, myocardial strain, coronary perfusion, and pulmonary pulsatility can all be evaluated with MRI.[98] PET is used in research settings to examine lung and RV metabolism as well as to image apoptosis in specialist facilities. When evaluating ventriculoarterial coupling and quantifying ventricular and arterial elastance, conductance catheterization is thought to be the gold-standard method.[5,43]

A comprehensive overview of normal echocardiographic readings for the right heart may be found at the American Society of Echocardiography.[99] According to the instructions, current echocardiographic references that have been modified for gender, ethnicity, and age are essential.[100] Based on these characteristics, normative equations for RV mass and systolic function have been constructed by the Multi-Ethnic Study of Atherosclerosis (MESA), which has a group of 4,204 individuals. Research conducted by Kawut and colleagues[100] has demonstrated that seniority and female sex are linked to higher RVEF, whereas a lower age, male sex, and Hispanic ethnicity usually correspond with larger RV mass.

Lately, studies have concentrated on dynamic measurements of the pulmonary circulation and right heart. These involve the RV reserve, which is usually measured by peak RVEF, peak stroke volume, or peak cardiac index after activity or pharmacological stress.[101,102] They additionally involve the mean pulmonary arterial pressure–cardiac output slope. The mean pulmonary arterial pressure–cardiac output slope in healthy individuals is typically less than 1.5 to 2.5 mm Hg·min/L; elderly people tend to have larger values.[22,103-113]

It is significant to remember that frequently employed RV systolic performance metrics, such tricuspid annular plane systolic excursion (TAPSE) and RVEF, are not direct measurements of ventricular contractility, but rather markers of ventriculoarterial coupling. This is especially important in PAH because of elevated contractility.[65] Furthermore, as TAPSE predominantly evaluates annular plane motion, which could be more influenced, changes in RVEF may not necessarily be reflected in the reduction in TAPSE following cardiac surgery.[114]

Prediction of Outcomes in Patients with Pulmonary Arterial Hypertension: The Importance of the Right Heart

A great deal of research has been done on predicting outcomes in pulmonary arterial hypertension (PAH) utilizing both small-scale investigations that include parameters from imaging and large-cohort designs.[115-123] Lifespan in PAH is consistently found to be closely associated with the right heart's ability to adjust to elevated pressure overload. Investigations on hemodynamics have shown that cardiac index and right atrial pressure are predictive.[7,14,117,118,124] The significance of tricuspid annular plane systolic excursion, RV myocardial performance index, atrial size, and pericardial effusion has been brought to light by echocardiographic research.[17,125] The predictive usefulness of stroke volume index, right ventricular ejection fraction, and indexed RV end-diastolic and end-systolic volumes is highlighted in magnetic resonance imaging investigations.[115,116,122,126] Delayed improvement has been linked to the severity of PAH, although its independent prognostic usefulness has not been established.[127] Recent study data indicates that RV strain can potentially be useful as a predictor.[17] Regarding cardiac biomarkers, a great deal of research has been done on B-type natriuretic peptide, N-terminal B-type natriuretic peptide, and troponin, all of which have been demonstrated to be outcome-predictive.[8,119,128-132] Of particular note are high-sensitivity troponin assays. The importance of peak oxygen consumption, right-to-left shunting, maximal cardiac index during physical activity, and the pulmonary pressure–cardiac output slope is highlighted by exercise testing.

Prospectively, new imaging indicators such right atrial function, ventricular strain, and myocardial acceleration during isovolumic contraction should be the main focus of future outcome investigations in PAH.[129,30] Furthermore, studies should be conducted to validate streamlined predicting scores that take into account several right cardiac imaging data. The objective of these endeavors is to augment the precision of outcome forecasts and elevate patient care in PAH.[48,101]

Management of Right Heart Failure: From Pulmonary Vasodilation to Targeted Right Ventricular Therapy

Authorized treatments for pulmonary arterial hypertension (PAH) cause the right heart to remodel in reverse in addition to increasing exercise tolerance and lowering pulmonary vascular resistance.[133] Vasodilatory or after-

load-reducing actions are the main mechanisms through which this remodelling is mediated. For instance, the widely prescribed vasodilator sildenafil may also have direct inotropic effects, however it is yet unclear whether this will be better for long-term clinical outcomes than endothelin receptor blockers. Yet another oral inotropic drug, digoxin, has been shown in a limited study to provide immediate hemodynamic advantages when administered sporadically for symptoms relief in PAH.[134]

Targeted medicines exclusively for the right heart have been the primary topic of recent research. These studies usually belong to two groups: new treatments targeted at right heart failure (RHF) and drugs shown 'to be helpful in left heart failure with a lower ejection fraction. Outcomes from research on left heart failure might not be immediately applicable to right heart failure '(RHF) because of the embryologic and molecular variations between the two hearts. Furthermore, a ventricle under pressure overload could react differently from one that is not.

The beneficial effects of bisoprolol and carvedilol on ventricular remodelling in PAH have been suggested by clinical research; however, in situations of severe PAH where contractile reserve is impaired, these advantages may not be as great.[135,136] According to a limited clinical research, capacity for exercise in patients with portopulmonary PAH may be negatively impacted by both selective and nonselective beta-blockade. Early research indicates that resynchronization therapy may have positive effects, and clinical trials are now being conducted to investigate these effects. Nevertheless, there hasn't been enough research done on the effects of angiotensin-converting enzyme inhibitors, angiotensin or aldosterone blockers, myosin activators, implantable defibrillators, or RV assist device installation on RHF and PAH.[137]

Metabolic regulation has showed potential for innovative targeted RV medication therapy. Phase 1 and phase 2 outcomes of clinical trials using mitochondrial modulators, such as dichloroacetate, are already available. However, further research is still needed on stem cell and gene treatments that particularly target the right heart in PAH patients.[138] Three important factors should be highlighted while handling acute RHF in patients with PAH. Avoid Volume Loading: Volume loading should be avoided in patients with increased filling pressures (right atrial pressure >10 to 15 mmHg) as it may deteriorate ventricular performance by increasing septal shift, prolonging the right ventricle, and incorporating pericardial constraint through ventricular interdependence. Stop Harmful Cycles: Inotropic or vasopressor support should be started as soon as possible to prevent hypercapnia or elevated intrathoracic pressure, as well as attempts to prevent increasing hypotension and ventricular ischemia. In serious instances, extracorporeal membrane oxygenation may be worth considering.

Decision Regarding Inotrope or Vasopressor: It is still uncertain which inotrope or vasopressor is best. Agents including levosimendan, norepinephrine, dopamine, and butamine are frequently employed.[2,139-141]

Role of Right Heart Investigation in the Development of Novel Pulmonary Arterial Hypertension Therapy

It is imperative that novel therapies produced for pulmonary arterial hypertension (PAH) undertake particular clinical trials for how they impact on the pressure-overloaded right heart, since treatments that target the pulmonary vasculature can have unexpected consequences on the functioning of the heart. Imatinib is one such medication that has demonstrated potential in treating pulmonary vascular remodelling. Research have shown that using it may have cardiotoxic side effects, though. The intricacy of medication effects in PAH is highlighted by this disparity.[142-143] Angiogenesis, apoptosis resistance, and cell proliferation characterize the altered pulmonary vasculature in PAH, whereas ischemia, capillary rarefaction, and cardiomyocyte apoptosis may have an impact on the collapsing right ventricle. Therefore, to guarantee overall treatment safety and effectiveness, any new PAH therapy needs to be thoroughly investigated for its advantages as well as its possible adverse impacts on the right sided heart.

Future Directions

This paper outlined recent developments in the knowledge of right heart failure (RHF) and highlighted a number of important areas that require more investigation. Improving the criteria of normal right cardiac anatomy and functioning is an essential since it will improve therapeutic options and diagnostic accuracy. It is essential to look into new genetic, epigenetic, and molecular processes connected to RHF in order to identify potential treatment targets and enhance current treatment strategies. Additionally, since certain patients may not respond to the current medications for refractory RHF, it is imperative to discover improved techniques for controlling this condition.

Any novel drug must be evaluated for both safety and efficacy in a laboratory environment on a right ventricle that is overloaded with pressure before moving on to clinical trials. In order to give a more thorough evaluation of the medication's effect on right heart health, clinical studies for pulmonary arterial hypertension (PAH) should also include parameters of right heart size and function as secondary outcomes. These actions are essential for developing more effective therapies and a comprehensive knowledge of RHF.

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